REMARKS

Claims 1-29 are pending in the instant application. Claims 1-29 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 1-7, 9-21, 23, and 26-29 stand rejected under 35 U.S.C. §103(a) as being unpatentably over United States Patent No. 6,103,492 to Yu in view of United States Patent No. 6,426,058 to Pines. Claim 8 stands rejected under 35 U.S.C. §103(a) as being unpatentably over United States Patent No. 6,103,492 to Yu in view of United States Patent No. 6,426,058 to Pines and further in view of United States Patent No. 5,834,226 to Maupin. Claim 22 stands rejected under 35 U.S.C. §103(a) as being unpatentably over United States Patent No. 6,103,492 to Yu in view of United States Patent No. 6,426,058 to Pines and further in view of United States Patent No. 6,278,893 to Ardenkjaer-Larson. Claims 24 and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentably over United States Patent No. 6,103,492 to Yu in view of United States Patent No. 6,426,058 to Pines and further in view of United States Patent No. 6,110,749 to Obremski. The application has been amended. Claims 1, 5, 14, 28 and 29 have been amended. Applicant respectfully submits that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

Claims 1-29 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These rejections are respectfully traversed.

The Examiner has objected that claim 1 is not clear and has stated that the preamble of the claim needs to set forth the purpose of the assay. In view of this, claim 1 has been amended as suggested by the Examiner to refer to an *in vitro* assay method to detect a physical or chemical change involving a chemical or biological species.

The Examiner has also objected that the term "1-10 defined positions" in claim 5 has insufficient antecedent basis. It is not clear to the Applicant exactly why this term is considered to lack antecedent basis and Applicant submits that the claim would be clear to

one of skill in the art, who would be well aware of the possible advantages of increasing the amount of detectable nucleus at certain positions in the assay reagent, for example, those positions closest to the site of the physical or chemical change which is being monitored by the assay. However, in view of the Examiner's objection, the claim has been amended to refer to "up to 10 defined positions". Applicant submits that this is clear.

Claim 14 was rejected for lacking antecedent basis for the term "the hyperpolarisation transfer". Applicant respectfully submits that as claim 14 no longer contains the term "the hyperpolarisation transfer", the rejection is obviated. Applicant notes that the claim has been amended to refer to step (b) of claim 1.

Claim 27 was rejected for lacking antecedent basis for the term "the well, surface or container". Applicant respectfully submits that the rejection has been obviated as claim 27 has been amended to read "a well, surface or container".

Claims 28 and 29 were rejected for depending from claim 1. Applicant respectfully submits that the rejection has been obviated as claims 28 and 29 have been amended so that they no longer refer to claim 1.

As each of the rejections under 35 U.S.C. §112 have been either traversed or obviated by amendment, Applicant respectfully requests reconsideration and withdrawal of the rejections.

The Examiner has rejected claims 1-7, 9-21, 23 and 26-29 as being unpatentable over Yu (US 6,103,492) in view of Pines *et al* (US 6,426,058). This rejection is respectfully traversed.

In particular, the Examiner objects that Yu discloses all of the essential features of claim 1 except for the hyperpolarisation of step (b). The Examiner refers to passages at column 40, column 8 and column 9 of Yu. The passage at column 40 relates to the detection

of an interaction between an agent and an opioid mu receptor. While this passages does suggest spectroscopy as a technique to detect the interaction it does not specifically mention NMR and does not give details of how the detection of the interaction could be carried out or even what would be detected. Furthermore, although the passage mentions the use of isotopically labelled reagents, it is not clear how Yu intends that these should be used. There is certainly no mention of their use as NMR active nuclei.

The cited passage on page 8 relates to a diagnostic assay kit for detecting the presence of an opioid mu receptor-like polypeptide in a sample. This is clearly a completely different assay from that described at column 40 as a different interaction is detected. Furthermore, it is an immunoassay and there is no suggestion that NMR could be used.

In view of these differences, Applicant respectfully submits that it is not appropriate to combine these two passages as they relate to completely different assay methods which are intended to detect completely different products by completely different methods.

Furthermore, the cited passage at column 9 merely teaches that the mu receptor-like polypeptide to which Yu relates can be used in a screening process to test the ability of a substance to interact with the opiod mu receptor. There are no details of any particular assay and no mention of NMR; the passage merely states that the interactions can be measured by any of a number of means known in the art.

In summary, Applicant submits that Yu fails to disclose, teach, or suggest any specific assay in which the steps (a) and (c) of claim 1 are carried out.

Applicants further submit that the teaching of Pines *et al* does not correct these deficiencies of Yu.

As Applicant has argued previously, Pines *et al* discloses a method of performing an assay using an assay reagent containing at least one NMR active nucleus which is

hyperpolarized and then analyzing the assay reagent and/or the assay by NMR. However, Pines *et al* does not disclose a method which includes the step of analyzing the assay reagent and/or the assay by NMR for a physical or chemical change in a biological species that is independent of the interaction of the biological species with the NMR active nucleus. As a result, Applicants respectfully submit that the combined teaching of Yu and Pines *et al* cannot lead to the method of claim 1 of the present application.

Although some of the NMR active nuclei of claims 2 and 3 are mentioned in the passage at column 40, lines 40-45 of Yu, Applicant reiterates that it is not even clear from this cited passage what is the purpose of these isotopes. There is certainly no clear teaching in Yu that they are intended to be detected by NMR.

With reference to claims 4 and 5, the passage at column 40, lines 40-45 of Yu does indeed suggest the use of labels. However, it is not clear whether these are even used as NMR active nuclei. There is certainly no teaching or suggestion that NMR active nuclei could be introduced into the assay reagent in selected positions of the molecule. The Examiner has argued that Yu is considered to disclose this feature because the wording "in 1-10 defined positions" is considered to be indefinite. Applicant is not clear why this is the case but has amended the claim to refer to "up to 10 defined positions". One of skill in the art of NMR would not consider this to be indefinite as such a person would understand that the NMR signal of a particular NMR active nucleus depends upon its environment and thus upon its specific position in a molecule. That person would also understand that it might be of use to enrich the concentration of an NMR active nucleus at one or more selected positions in the assay reagent molecule in order to enhance the signal obtained from that position of the assay reagent. For example, it might be advantageous to enrich the concentration of NMR active nucleus at a site close to that of the physical or chemical change being detected.

The passage from Yu at column 8, lines 57 to 58 refers specifically to radioactive labels for antibodies in an immunoassay. It does not relate to NMR and is therefore completely irrelevant to the present invention.

Furthermore, there is no teaching in Yu which suggests that any of the assay methods it describes are deficient in any way or require improvement. There is also no suggestion in Pines *et al* that the method it describes could be used to detect a physical or chemical change in a biological species that it is independent of the interaction of the biological species with the NMR active nucleus.

Applicant respectfully submit, therefore, that a person of skill in the art of assay methods would have had no motivation to combine the teachings of Yu and Pines *et al.*

Although aspects of claims 6,7, 9-21 and 26-29 are disclosed in Yu or Pines *et al*, these claims are all dependent on claim 1 and, as argued above, Applicants respectfully submit that claim 1 is patentably distinct over Yu in view of Pines *et al.*

The Examiner has rejected claim 8 as being unpatentable over Yu in view of Pines *et al* as applied to claim 1 and further in view of Maupin (US 5,834,226). This rejection is respectfully traversed.

Applicant has already provided arguments concerning the non-obviousness of claim 1 and respectfully submits that Maupin does not supply the missing features. Maupin does not relate to an assay in which a physical or chemical change in a biological species is monitored by NMR. It teaches that the formation of sulfite ion is preferably visually monitored by its reaction with a coloured organic dye (column 4, lines 40-42). The only other detection methods mentioned are the formation of a visible precipitate, a fluorescent or chemiluminescent signal or a change in pH or ionic strength of the solution (column 8, lines 50-67). Applicant therefore respectfully submits that the teaching of Maupin is not relevant to the present application as it does not relate to an assay which is monitored by NMR. Indeed, it seems likely that it would be difficult to monitor the reaction to which Maupin relates by NMR.

The Examiner has rejected claim 22 as being unpatentable over Yu in view of Pines *et al* as applied to claim 1 and further in view of Ardenkjaer-Larson *et al*. This rejection is respectfully traversed.

However, as already discussed above, Applicant submits that claim 1 is non-obvious over Yu and Pines *et al*. Applicant further submits that Ardenkjaer-Larson *et al* does not supply the missing features since it fails to disclose an analysis of a physical or chemical change in a biological species that is independent of the interaction of the biological species with the NMR active nucleus.

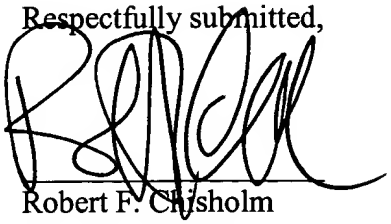
The Examiner has rejected claims 24 and 25 as being unpatentable over Yu in view of Pines *et al* as applied to claim 1, and further in view of Obremski (US 6,110,749). This rejection is respectfully traversed.

Obremski relates to a system for simultaneously conducting multiple ligand binding assays on a sample possibly containing target analytes, wherein a complex between a specific binding partner at a probe and target analyte is detected using evanescent waves and light-responsive compounds or compounds. It can be seen, therefore that the method of Obremski does not include detection by NMR and, furthermore that it could not include detection by NMR. In view of this, Applicant submits that it is not relevant to the method of the present invention, in which detection is by NMR.

In view of the above arguments, Applicant respectfully submits that the present application, including claims 1-29, are patentably distinct over the prior art. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,



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